How Clinically Relevant is Dapsone-related Peripheral Neuropathy?

An Overview of Available Data with Emphasis on Clinical Recognition

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Dapsone, first developed in 1908, was initially intended for oral treatment of infectious diseases; however, dapsone was later shown to have potent anti-inflammatory properties.[1,2] The anti-inflammatory mechanisms of dapsone appear to be separate from its antibacterial properties. Oral dapsone has been shown to be efficacious for dermatoses with neutrophilic infiltration, which is believed to be related to stabilization of neutrophil lysosomes and disruption of adherence properties of neutrophils.[1,2]

Several dermatological conditions are treated with dapsone, including leprosy, acne conglobata, dermatitis herpetiformis (as first-line treatment), pemphigoid, pemphigus, erythema elevatum diutinum, polychondritis, leucocytoclastic vasculitis, and Behcet's disease.[3–6] Dapsone is a second-line treatment for *Pneumocystis jiroveci* pneumonia.[7]

Oral dapsone therapy is associated with a constellation of hematological adverse reactions. The most common of these include hemolytic anemia (usually secondary to glucose-6-phosphate dehydrogenase [G6PD] deficiency), methemoglobinemia, and agranulocytosis. These more common side effects typically appear during the early phase of treatment and are dose related.[6] Due to the heavy emphasis on monitoring for hematological side effects associated with oral dapsone use, neurological adverse reactions are likely to remain unrexognized, especially early in the course of their emergence. Neurological side effects of oral dapsone include ocular adverse effects, such as optic atrophy, and sensory and motor neuropathies.[5,8]

Dapsone-related peripheral neuropathy, although an uncommon side effect of oral treatment, is clinically significant due to its frequent subtle onset (especially with motor neuropathy) and the high potential for long-term persistence, including after cessation of dapsone intake.[5] The onset of peripheral neuropathy after initiation of oral dapsone therapy is variable.[5]

Guidelines for monitoring the hematologic adverse effects of oral dapsone are in place, but are lacking for neurological side effects, such as peripheral neuropathy.[2] Little direction for monitoring the neurological side effects of oral dapsone is provided in the literature. This article discusses various reports of neuropathies and the subtle initial symptoms that clinicians need to be cognizant of during treatment.

What is the pathophysiology theorized in peripheral neuropathy related to oral dapsone use?

The mechanism has not been proven; however, several theories exist. The most popular theory suggests there is a direct neurotoxic effect due to the ability of dapsone to concentrate in neural tissue.[4]

What types of neuropathy have been reported?

Motor neuropathy related to oral dapsone use was first reported in 1969 in two patients treated for pyoderma grangrenosum and acne conglobata.[4] The data reported patients exhibiting loss of fine

motor skills and gait disturbances. Atrophy of thenar eminence and interosseous muscles, as well as toe/foot drop, and sock and glove sensation loss have been reported.[10] Motor neuropathy is more common than sensory neuropathy with oral dapsone use, although both have been reported to occur simultaneously. The lower extremities have been affected more often than the upper extremities in the cases reported.[5] Nerve conduction studies of affected individuals demonstrated abnormalities of the compound muscle action potentials with diminished amplitudes in lower extremities as compared to upper extremities. In addition, the conduction velocity and distal latencies are mildly prolonged. These findings are consistent with axonal atrophy with few features of secondary demyelination. Interestingly, this neuropathic pattern is also common to lead-induced peripheral neuropathy.[10]

Is there an associated dosage or treatment duration implicated in causing neuropathy associated with oral dapsone use?

Neuropathy associated with oral dapsone is reported more commonly after prolonged therapy, usually over at least a few years of use. However, neuropathy has been reported to occur as early as within six weeks of oral dapsone use.[4] Cumulative dosages ranging from 25 to 600g are seen more commonly; however, there are reports of doses as little as 4g eliciting neuropathic side effects.[4]

What is the average resolution time of dapsone-related peripheral neuropathy?

In many cases, symptoms of dapsone-related neuropathy largely resolve over 12 months after cessation of oral dapsone with no permanent axon demyelination. However, some patients demonstrated neuropathic symptoms up to three years after stopping oral dapsone.[5]

Is dapsone-induced peripheral neuropathy related to the metabolic acetylator status of the patient?

Studies have suggested there is no relationship between metabolic acetylator status of the patient and dapsone blood levels although this was once theorized to be a possible etiology for side effects of dapsone.[11,12]

Does co-administration with cimetidine prevent peripheral neuropathy?

Due to enzyme inhibition, cimetidine may shunt the metabolism of dapsone to greater production of nontoxic inactive metabolites.[2] At present, it is not clear whether concomitant use of oral cimetidine with oral dapsone can reduce the risk of development of neuropathy. More research is needed to prove if oral cimetidine may prevent the development of dapsone-related peripheral neuropathy.[2]

What steps may be taken to prevent peripheral neuropathy side effects associated with oral dapsone use?

Patient education is a vital component related to recognition of neuropathic side effects. Realistic explanation of side effects of oral dapsone is important with emphasis placed on early detection of symptoms and signs of toxicity. Specific questions directed toward loss of fine motor function, such as issues with the ability to button shirts, can be an early indicator.[10] Early signs can be subtle and clinicians are advised to exercise a high index of suspicion for development of peripheral neuropathy. Therefore, a baseline assessment of motor and sensory peripheral neurological function is suggested along with reassessment throughout oral dapsone treatment, especially as clinical emergence may be subtle and slowly progressive.

What measures may be used to assess patients on oral dapsone treatment if a peripheral neuropathy is suspected?

Though nerve conduction and electromyographic (EMG) studies are the gold standards, these tests are not necessary for screening to assess motor and sensory loss. It is suggested that physical examination include the assessment of sensory function with a 10g filament and vibration sense with a 128Hz tuning fork.[10] Testing the first halux with a tuning fork for 8 to 10 seconds can be used to assess for generalized peripheral neuropathy. Muscle strength testing should be consecutive in order to assess muscle fatigability commonly seen with peripheral neuropathy. The presence of an Achilles tendon reflex suggests absence of diffuse involvement. Gait analysis and unipedal stance may be the most sensitive and specific tests to monitor motor neuropathy involving the lower extremities.[10] Repeated clinical examination of the hands over time to comparatively evaluate for signs of muscle wasting, especially of thenar eminences, may be valuable in detecting unrecognized motor neuropathy; however, this would suggest progressive involvement.

What conclusions can be drawn from the data available on dapsone-related peripheral neuropathy?

Due to the variable time frame and wide cumulative dose ranges associated with motor and sensory neuropathy, it is important to initially assess a baseline neurological assessment before oral dapsone therapy is initiated. Periodic reassessment of patients is suggested throughout therapy. Resolution of neuropathy generally occurs over one year of discontinuing dapsone therapy, although more prolonged cases of neuropathy have been reported.[6] Clinicians focus on potential hematological side effects when initiating oral dapsone therapy for good reason. However, the potential for peripheral neuropathy must be kept top of mind, especially due to the subtle and slowly progressive development observed in many cases.

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